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(54) Title: PHARMACEUTICAL FORMULATION COMPRISING NON-PEPTIDE RENIN INHIBITOR AND SURFACTANT

(57) Abstract: Composition comprising (1) a non-peptide renin inhibitor which is poorly soluble to readily soluble in water and (2) at least one physiologically tolerated anionic surfactant, at least one physiologically tolerated amphoteric surfactant, at least one physiologically tolerated neutral surfactant, or a mixture of at least two of these surfactants, with the quantity of readily soluble renin inhibitor being at least 10% by weight, and the quantity of a poorly soluble renin inhibitor being at least 35% by weight, based on the composition. In oral administration forms, the composition exhibits increased bioavailability.

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PHARMACEUTICAL FORMULATION COMPRISING NON-PEPTIDE RENIN INHIBITOR AND SURFACTANT

The present invention relates to a composition consisting of a non-peptide renin inhibitor and an anionic, amphoteric or neutral surfactant, to oral administration forms comprising this composition, and to a method for improving the bioavailability of non-peptide renin inhibitors.

Non-peptide renin inhibitors are valuable compounds for treating high blood pressure, for example, and other cardiovascular diseases. A variety of these compounds have recently been disclosed. EP-A-0 716 077, WO 01/09083, WO 02/08172 and WO 02/02508 describe ω-phenyloctanecarboxamide derivatives which are very highly soluble in water. Il Farmaco 56 (2001), pages 21-27, describes piperidine derivatives. Bioorganic & Medicinal Chemistry Letters (1996) Volume 6, pages 1589-1594; Arzneimittelforschung (1993), 43(2a), pages 260 to 262; Am. J. Hypertens. (1996), 9(6), pages 517-522 and Xenobiotica (1996), 26(3), pages 33-345 propose imidazole derivatives. Circulation (1995), 91(2), pages 330-338; Clin. Pharmacol. Ther. (St. Louis) (1995), 57(3), pages 342-348 and Tetrahedron (1999), 55(15), pages 4763-4768 describe thiazole derivatives as renin inhibitors.

Although non-peptide renin inhibitors have been known for a relatively long time and possess outstanding pharmacological properties and a very high degree of activity, they have not thus far been demonstrated to be suitable for broad therapeutic application, for example for treating high blood pressure using oral administration forms. The main reason lies in the low degree of bioavailability following oral administration, as is reported by various authors in Il Farmaco 56 (2001), pages 21-27; Chemistry & Biology 2000, 7:493-504; Clin. Pharmacokinet. (1995), 29(1), pages 6-14 and Pharmac. Ther. (1994); Volume 61, pages 325-344. The low degree of oral bioavailability also still continues to restrict therapeutic application. It would therefore be extremely desirable to identify a galenic formulation which exhibits higher bioavailability and which can therefore be used to reduce the high requirement for material (high doses) in order, in this way, to provide suitable forms for oral administration. It is thereby also possible, where appropriate, to obtain an improvement in the case of active compounds which are less well tolerated in order, in this way, to make it possible to achieve a broader therapeutic application for the renin inhibitors.

The use of surfactants as wetting agents in oral drug forms is described in the literature, for example in H. Sucker, P. Fuchs, P. Speiser, Pharmazeutische Technologie, 2nd edition, Thieme 1989, page 260. It is known from other papers, such as published in Advanced Drug Delivery Reviews (1997), 23, pages 163-183, that it is also possible to use surfactants, inter alia, to improve the permeation and bioavailability of pharmaceutical active compounds; however, this effect does not occur in the case of all active compounds and the extent of the improvement is frequently very slight.

It has now been found, surprisingly, that it is possible to substantially increase the bioavailability of both non-peptide renin inhibitors which are poorly soluble in water and such inhibitors which are particularly readily soluble in water if these inhibitors are mixed with anionic, amphoteric or neutral surfactants and processed into oral administration forms. The effect is particularly surprising in the case of water-soluble renin inhibitors since water-soluble active compounds are not as a rule formulated in combination with surfactants. The effect is also unexpectedly high, because a substantial increase of the bioavailability has been achieved. The increase of bioavailability is so important that therapeutic application is made possible in more well-tolerated doses and/or in more attractive oral dosage forms.

The invention firstly relates to a composition comprising (1) a non-peptide renin inhibitor which is of relatively high molecular weight (MW 500-800) and which is poorly soluble or readily soluble in water and (2) at least one physiologically tolerated anionic surfactant, at least one physiologically tolerated amphoteric surfactant, at least one physiologically tolerated neutral surfactant, or a mixture of at least two of these surfactants, with the quantity of readily soluble renin inhibitor being at least 10% by weight, and the quantity of a poorly soluble renin inhibitor being at least 35% by weight, based on the composition.

Within the context of the invention, readily soluble in water denotes that at least 1 g, preferably at least 30 g, and particularly preferably at least 100 g, of renin inhibitor are dissolved per 100 ml of water. Within the context of the invention, poorly soluble in water denotes that less than 1 g, preferably at most 100 mg, and particularly preferably at most 10 mg, of renin inhibitor are dissolved per 100 ml of water.

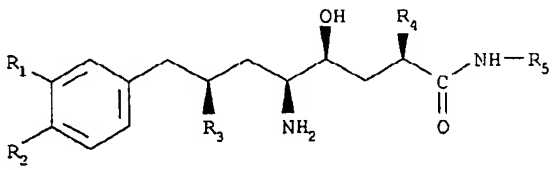
Within the context of the invention, non-peptide means that a renin inhibitor is not only composed of aminocarboxylic acids.

The quantity of readily soluble renin inhibitors can, for example, be from 10 to 90% by weight, preferably from 20 to 90% by weight, particularly preferably from 50 to 90% by weight, and in particular preferably from 60 to 90% by weight, based on the composition.

The quantity of poorly soluble renin inhibitors can, for example, be from 40 to 90% by weight, preferably from 50 to 90% by weight, particularly preferably from 60 to 90% by weight, and in particular preferably from 70 to 90% by weight, based on the composition.

Non-peptide renin inhibitors are known and are described in the literature mentioned at the outset.

ω-Phenyloctanecarboxamide derivatives are described in EP-A-0 716 077, WO 01/09083, WO 02/08172 and WO 02/02508. ω-Phenyloctanecarboxamide derivatives are preferably those of the formula I,



(I),

in which

R_1 and R_2 are, independently of each other, H, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, or C_1-C_6-alkoxy-C_1-C_6-alkyloxy, R_3 is C_1-C_6-alkyl, R_4 is C_1-C_6-alkyl, and R_5 is C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkanoyloxy-C_1-C_6-alkyl, C_1-C_6-aminoalkyl, C_1-C_6-alkylamino-C_1-C_6-alkyl, C_1-C_6-dialkylamino-C_1-C_6-alkyl, C_1-C_6-alkanoylamido-C_1-C_6-alkyl, HO(O)C-C_1-C_6-alkyl, C_1-C_6-alkyl-O-(O)C-C_1-C_6-alkyl, H_2N-C(O)-C_1-C_6-alkyl, C_1-C_6-alkyl-HN-C(O)-C_1-C_6-alkyl or $(C_1$-C_6-alkyl$)_2$N-C(O)-C_1-C_6-alkyl.

R_1 and R_2 can, as alkyl, be linear or branched and preferably contain from 1 to 4 C atoms. Examples are methyl, ethyl, n- and i-propyl, n-, i- and t-butyl, pentyl and hexyl.

R_1 and R_2 can, as haloalkyl, be linear or branched and preferably contain from 1 to 4, particularly preferably 1 or 2, C atoms. Examples are fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-chloroethyl and 2,2,2-trifluoroethyl.

R_1 and R_2 can, as alkoxy, be linear or branched and preferably contain from 1 to 4 C atoms. Examples are methoxy, ethoxy, n- and i-propyloxy, n-, i- and t-butyloxy, pentyloxy and hexyloxy.

R_1 and R_2 can, as alkoxyalkyl, be linear or branched. The alkoxy group preferably contains from 1 to 4, and particularly 1 or 2, C atoms and the alkyl group preferably contains from 1 to 4 C atoms. Examples are methoxymethyl, 1-methoxyeth-2-yl, 1-methoxyprop-3-yl, 1-methoxybut-4-yl, methoxypentyl, methoxyhexyl, ethoxymethyl, 1-ethoxyeth-2-yl, 1-ethoxyprop-3-yl, 1-ethoxybut-4-yl, ethoxypentyl, ethoxyhexyl, propyloxymethyl, butyloxymethyl, 1-propyloxyeth-2-yl and 1-butyloxyeth-2-yl.

R_1 and R_2 can, as C_1-C_6-alkoxy-C_1-C_6-alkyloxy, be linear or branched. The alkoxy group preferably contains from 1 to 4, and particularly 1 or 2, C atoms and the alkyloxy group preferably contains from 1 to 4 C atoms. Examples are methoxymethyloxy, 1-methoxyeth-2-yloxy, 1-methoxyprop-3-yloxy, 1-methoxybut-4-yloxy, methoxypentyloxy, methoxyhexyloxy, ethoxymethyloxy, 1-ethoxyeth-2-yloxy, 1-ethoxyprop-3-yloxy, 1-ethoxybut-4-yloxy, ethoxypentyloxy, ethoxyhexyloxy, propyloxymethyloxy, butyloxymethyloxy, 1-propyloxyeth-2-yloxy and 1-butyloxyeth-2-yloxy.

In a preferred embodiment, R_1 is methoxy- or ethoxy-C_1-C_4-alkyloxy, and R_2 is preferably methoxy or ethoxy. Very particular preference is given to compounds of formula I in which R_1 is 1-methoxyprop-3-yloxy and R_2 is methoxy.

R_3 and R_4 can, as alkyl, be linear or branched and preferably contain from 1 to 4 C atoms. Examples are methyl, ethyl, n- and i-propyl, n-, i- and t-butyl, pentyl and hexyl. In a preferred embodiment, R_3 and R_4 are in each case isopropyl in the compounds of the formula I.

R_5 can, as alkyl, be linear or branched and preferably contain from 1 to 4 C atoms. Examples of alkyl have been mentioned previously. Preference is given to methyl, ethyl, n- and i-propyl, and n-, i- and t-butyl.

R_5 can, as C_1-C_6-hydroxyalkyl, be linear or branched and preferably contain from 2 to 6 C atoms. Some examples are 2-hydroxyeth-1-yl, 2-hydroxyprop-1-yl, 3-hydroxyprop-1-yl, 2-, 3- or 4-hydroxybut-1-yl, hydroxypentyl and hydroxyhexyl.

R_5 can, as C_1-C_6-alkoxy -C_1-C_6-alkyl, be linear or branched. The alkoxy group preferably contains from 1 to 4 C atoms and the alkyl group preferably contains from 2 to 4 C atoms. Some examples are 2-methoxyeth-1-yl, 2-methoxyprop-1-yl, 3-methoxyprop-1-yl, 2-, 3- or 4-methoxybut-1-yl, 2-ethoxyeth-1-yl, 2-ethoxyprop-1-yl, 3-ethoxyprop-1-yl, and 2-, 3- or 4-ethoxybut-1-yl.

R_5 can, as C_1-C_6-alkanoyloxy-C_1-C_6-alkyl, be linear or branched. The alkanoyl group preferably contains from 1 to 4 C atoms and the alkyl group preferably contains from 2 to 4 C atoms. Some examples are formyloxymethyl, formyloxyethyl, acetyloxyethyl, propionyloxyethyl and butyroyloxyethyl.

R_5 can, as C_1-C_6-aminoalkyl, be linear or branched and preferably contain from 2 to 4 C atoms. Some examples are 2-aminoethyl, 2- or 3-aminoprop-1-yl and 2-, 3- or 4-aminobut-1-yl.

R_5 can, as C_1-C_6-alkylamino-C_1-C_6-alkyl and C_1-C_6-dialkylamino-C_1-C_6-alkyl, be linear or branched. The alkylamino group preferably contains C_1-C_4-alkyl groups and the alkyl group preferably contains from 2 to 4 C atoms. Some examples are 2-methylaminoeth-1-yl, 2-dimethylaminoeth-1-yl, 2-ethylaminoeth-1-yl, 2-diethylaminoeth-1-yl, 3-methylaminoprop-1-yl, 3-dimethylaminoprop-1-yl, 4-methylaminobut-1-yl and 4-dimethylaminobut-1-yl.

R_5 can, as C_1-C_6-alkanoylamido-C_1-C_6-alkyl, be linear or branched. The alkanoyl group preferably contains from 1 to 4 C atoms and the alkyl group preferably contains from 1 to 4 C atoms. Some examples are 2-formamidoeth-1-yl, 2-acetamidoeth-1-yl, 3-propionylamidoeth-1-yl and 4-butyroylamidoeth-1-yl.

R_5 can, as HO(O)C-C_1-C_6-alkyl, be linear or branched and the alkyl group preferably contains from 2 to 4 C atoms. Some examples are carboxymethyl, carboxyethyl, carboxypropyl and carboxybutyl.

R_5 can, as C_1-C_6-alkyl-O-(O)C-C_1-C_6-alkyl, be linear or branched, and the alkyl groups preferably contain, independently of each other, from 1 to 4 C atoms. Some examples are methoxycarbonylmethyl, 2-methoxycarbonyleth-1-yl, 3-methoxycarbonylprop-1-yl, 4-methoxycarbonylbut1yl, ethoxycarbonylmethyl, 2-ethoxycarbonyleth-1-yl, 3-ethoxy-carbonylprop-1-yl and 4-ethoxycarbonylbut-1-yl.

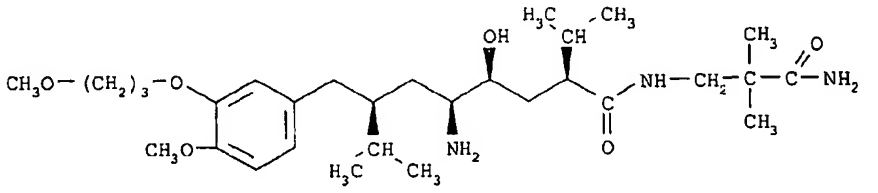
R_5 can, as H_2N-C(O)-C_1-C_6-alkyl, be linear or branched, and the alkyl group preferably contains from 2 to 6 C atoms. Some examples are carbamidomethyl, 2-carbamidoeth-1-yl, 2-carbamido-2,2-dimethyleth-1-yl, 2- or 3-carbamidoprop-1-yl, 2-, 3- or 4-carbamidobut-1-yl, 3-carbamido-2-methylprop-1-yl, 3-carbamido-1,2-dimethylprop-1-yl, 3-carbamido-3-methylprop-1-yl, 3-carbamido-2,2-dimethylprop-1-yl, 2-, 3-, 4- or 5-carbamidopent-1-yl, or 4-carbamido-3,3- or -2,2-dimethylbut-1-yl.

R_5 can, as C_1-C_6-alkyl-HN-C(O)-C_1-C_6-alkyl or $(C_1$-C_6-alkyl$)_2$N-C(O)-C_1-C_6-alkyl, be linear or branched, and the NH-alkyl group preferably contains from 1 to 4 C atoms, and the alkyl group preferably contains from 2 to 6 C atoms. Examples are the previously mentioned carbamidoalkyl groups whose N atom is substituted by one or two methyl, ethyl, propyl or butyl.

A preferred subgroup of compounds of formula I is formed by those in which R_1 is C_1-C_4-alkoxy or C_1-C_4-alkoxy-C_1-C_4-alkyloxy, R_2 is C_1-C_4-alkoxy, R_3 is C_1-C_4-alkyl, R_4 is C_1-C_4-alkyl and R_5 is optionally N-mono- or N-di-C_1-C_4-alkyl-substituted $H_2NC(O)$-C_1-C_6-alkyl.

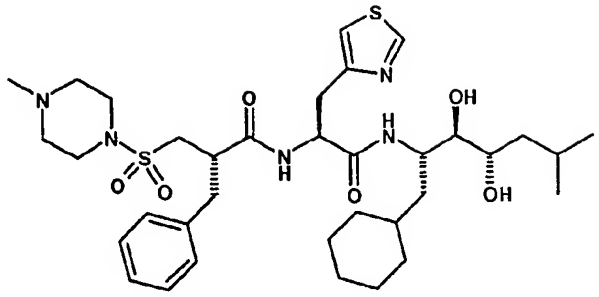
A more preferred subgroup of compounds of the formula I is formed by those in which R_1 is methoxy-C_2-C_4-alkyloxy, R_2 is methoxy or ethoxy, R_3 is C_2-C_4-alkyl, R_4 is C_2-C_4-alkyl and R_5 is $H_2NC(O)$-C_1-C_6-alkyl.

The ω-phenyloctanecarboxamide derivative which is very particularly preferred is the compound of the formula Ia,



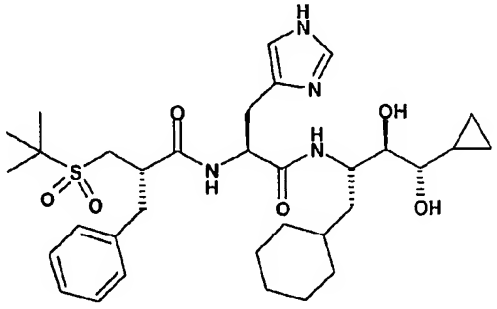
(Ia).

The compound of the formula (A), which is also known as Zankiren, may be mentioned as a representative of thiazole derivatives:



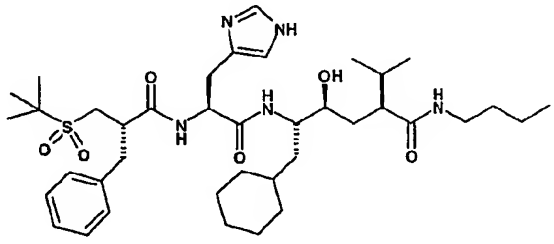
(A).

The compound of the formula (B), which is also known as Remikiren, may be mentioned as a representative of imidazole derivatives:



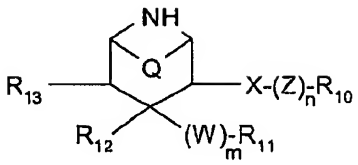
(B).

Another representative of imidazole derivatives is the compound of the formula (C):



(C).

Representatives of a piperidine derivative which may be mentioned are compounds of formula D (see also WO 00/64873, WO 00/64887 and WO 97/09311),



(D),

in which

R_{10} is aryl or heteroaryl or heterocycloalkyl or heterocycloalkenyl, and

R_{11} is phenyl, naphthyl, acenaphthyl, cyclohexyl, pyridyl, pyrimidyl, pyrazinyl, oxopyridinyl, diazinyl, triazolyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, pyrrolyl or furyl which are unsubstituted or substituted by from one to three halogen, hydroxyl, cyano, trifluoromethyl, lower alkyl, halo-lower alkyl, hydroxyl-lower alkyl, lower alkoxy-lower alkyl, cyano-lower alkyl, carboxyl-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxycarbonyloxy-lower alkyl, lower alkoxycarbonyl or lower alkoxy groups or a lower alkylenedioxy group, and/or by a radical L_1-T_1-L_2-T_2-L_3-T_3-L_4-T_4-L_5-T_5-U;

L_1, L_2, L_3, L_4 and L_5 are, independent of each other, a bond, C_1-C_8-alkylene, C_2-C_8-alkenylene or C_2-C_8-alkynylene, or are absent;

T_1, T_2, T_3, T_4 and T_5 are, independent of each other,

(a) a bond or are absent or are one of the groups

(b) –CH(OH)–

(c) –(CHOR$_{15}$)–

(d) –(CHNR$_{14}$ R$_{15}$)–

(e) –CO-

(f) -CR$_{16}$ R$_{17}$-

(g) –O- oder –NR$_{15}$-

(h) –S(O)$_{0-2}$

(i) –SO$_2$NR$_{15}$-

(j) –NR$_{15}$SO$_2$-

(k) –CONR$_{15}$-

(l) –NR$_{15}$CO-

(m) –O-CO-

(n) –CO-O-

(o) –O-CO-O-

(p) –O-CO-NR$_{15}$-

(q) –NR$_{15}$-CO-NR$_{15}$-

(r) –NR$_{15}$-CO-O-,

where the bonds issuing from (b), (d), (e) and (g) to (r) lead to a C atom of the adjacent group and this C atom is saturated if the bond issues from a heteroatom and where not more than two groups (b) to (f), three groups (g) to (h) and one group (i) to (r) are present;

R_{12} is hydrogen, hydroxyl, lower alkoxy or lower alkenyloxy;

R_{13} is hydrogen, lower alkyl, lower alkenyl, lower alkoxy, hydroxy-lower alkyl, benzyl, oxo or a group R_{18}-Z_1-X_1-, where R_{18} is

(a) H-

(b) lower alkyl

(c) lower alkenyl

(d) hydroxyl-lower alkyl

(e) polyhydroxyl-lower alkyl

(f) lower alkyl-O-lower alkyl

(g) aryl

(h) heteroaryl or heterocycloalkyl or heterocycloalkenyl

(i) aralkyl

(j) heteroaryl- or heterocycloalkyl- or heterocycloalkenyl-lower alkyl

(k) aryloxy-lower alkyl

(l) heteroaryloxy- or heterocycloalkyloxy- or heterocycloalkenyloxy-lower alkyl

(m) $R_{14}R_{15}N$-$(CH_2)_{1-3}$-

(n) $R_{14}R_{15}N$-

(o) lower alkyl-$S(O)_{0-2}$-

(p) aryl-$S(O)_{0-2}$-

(q) heteroaryl-$S(O)_{0-2}$- or heterocycloalkyl-$S(O)_{0-2}$- or heterocycloalkenyl-$S(O)_{0-2}$-

(r) HO-SO_3- or its salts

(s) H_2N-C(NH)-NH-

(t) NC-

and the bonds issuing from (n) to (t) lead to a C atom of the adjacent groups and this C atom is saturated if the bond issues from a heteroatom;

Z_1 is

(a) a bond, is absent or is one of the groups

(b) lower alkylene

(c) lower alkenylene

(d) –O-, -NR_{19}- or -$S(O)_{0-2}$

(e) -CO-

(f) –CO-O-

(g) –O-CO-O-

(h) –O-CO-NR_{19}-

(i) -NR_{19}-CO-O-

(j) -O-CO-NR_{19}-

(k) -NR_{19}-CO-

(l) -NR_{19}-CO-NR_{19}-

(m) –CH(OR_{20})-

and the bonds issuing from (d) and (f) to (m) lead to a C atom of the adjacent group and this C atom is saturated if the bond issues from a heteroatom;

X_1 is

(a) a bond, is absent or is one of the groups

(b) –O-

(c) –NR_{19}-

(d) –$S(O)_{0-2}$-

(e) –$(CH_2)_{1-3}$-;

or R_{12} and R_{13} are together a bond;

R_{14} and R_{15} are hydrogen, lower alkyl, lower alkenyl, aryl-lower alkyl or acyl, or, together with the N atom to which they are bonded, are a five-membered or six-membered heterocyclic ring which can contain an additional N, O or S atom, with the additional N atom optionally being substituted by lower alkyl;

R_{16} and R_{17}, together with the C atom to which they are bonded, are a three-membered to seven-membered ring which can contain one or two O or S atoms or -O- or -SO_2- groups;

R_{19} is hydrogen or lower alkyl,

R_{20} is hydrogen, lower alkyl, acyl or aralkyl;

R_{21} is carboxyalkyl, alkoxycarbonylalkyl, alkyl or hydrogen;

U is hydrogen, lower alkyl, cycloalkyl, cyano, optionally substituted cycloalkyl, aryl, heteroaryl or heterocycloalkyl or heterocycloalkenyl;

Q is ethylene or is absent,

X is a bond, oxygen, sulfur or groups –CH-R_{19}-, –CHOR_{20}, -O-CO-, -CO- or –C=NOR_{21}; where the bond issuing from an oxygen atom or sulfur atom leads to a saturated C atom of the group Z or to R_{10};

W is oxygen or sulfur;

Z is lower alkylene, lower alkenylene, hydroxyl-lower alkylidene, -O-, -S-, -O-Alk-, -S-Alk-, -Alk-O- or –Alk-S-, where Alk is lower alkylene; and where

a) if Z is -O- or –S-, X is –CH-R_{19}- and either R_{11} contains a substituent L_1-T_1-L_2-T_2-L_3-T_3-L_4-T_4-L_5-T_5-U or R_{13} is a substituent which is defined as above and which is different from hydrogen;

b) if Z is –O-Alk- or –S-Alk-, X is –CH-R_{19}-; and

c) if X is a bond, Z is lower alkylene, lower alkenylene, -Alk-O- or –Alk-S-;

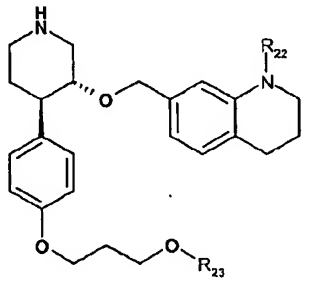
n is 1 or, if X is –O-CO-, is 0 or 1;

m is 0 or 1;

and pharmaceutically utilizable salts thereof.

The term "lower" denotes a content of from 1 to 6, and preferably from 1 to 4, C atoms.

A preferred subgroup of the compounds of the formula D is formed by those of the formula E



(E),

in which

R_{22} is

(a) –$(CH_2)_k$-$NR_{24}R_{25}$ and k is 2, 3 or 4;

(b) –$(CH_2)_k$-OR_{24} and k is 2, 3 or 4;

(c) –$(CH_2)_m$-OR_{26} and m is 1 or 2; or

(d) –$(CH_2)_l$-R_{27} and l is 1, 2 or 3;

R_{23} is cycloalkyl-lower alkyl, 1,1,1-trifluoroethyl, phenyl or benzyl, or phenyl or benzyl which is substituted by one to three halogen, cyano, C_1-C_3-alkoxy or nitro;

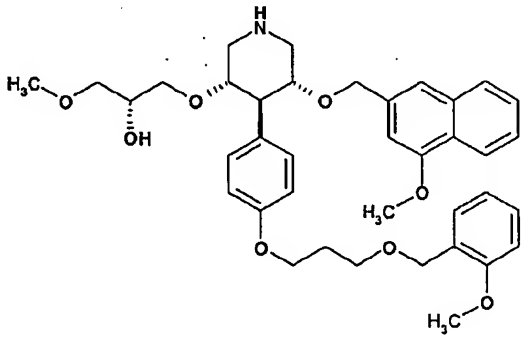
R_{24} is hydrogen or C_1-C_3-alkyl;

R_{25} is hydrogen, C_1-C_3-alkyl, C_1-C_3-alkylsulfonyl, aminosulfonyl, C_1-C_3-alkylaminosulfonyl, C_1-C_3-alkylaminocarbonyl, C_1-C_3-alkylcarbonyl, trifluoromethylcarbonyl, trifluoromethylsulfonyl or aminocarbonyl;

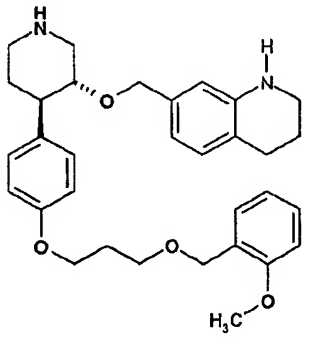
R_{26} is C_1-C_3-alkoxycarbonyl, aminocarbonyl, C_1-C_3-alkylaminocarbonyl, di-C_1-C_3-alkylamino-carbonyl or cyano;

R_{27} is imidazolyl or triazolyl, with the proviso that I is 2 or 3 when imidazolyl or triazolyl is bonded by way of a C-N bond;
and pharmaceutically utilizable salts thereof.

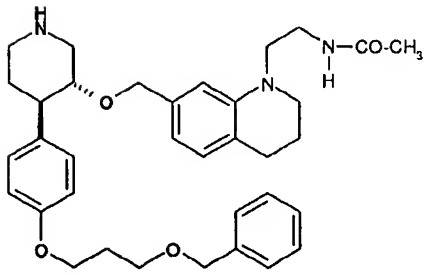
Some specific examples are piperidine derivatives of the formulae F, G and H:



(F),



(G),



(H).

The compounds of the formulae A to H, I and Ia can also be present as salts, for example of monocarboxylic or dicarboxylic acids. Particular preference is given to hemifumarates and succinates. (The hemifumarate of the formula Ia is termed SPP100B below. The succinate of the formula F is termed SPP500A below).

The renin inhibitors are relatively large molecules. The compounds of formulae A to H are poorly soluble in water; by contrast, ω-phenyloctanecarboxamide derivatives, particularly of the formula Ia, are very readily soluble in water. All these properties suggest low oral bioavailability.

Physiologically tolerated anionic and neutral surfactants are known as auxiliary substances in oral formulations of pharmaceutical active compounds and are listed, for example, in the American Code of Federal Regulations Title 21 (Food and Drugs), revised 1 April 2001.

Anionic surfactants are widely known. They are mainly organic acids and their physiologically tolerated salts, such as alkali metal salts (Na or K) or alkaline earth metal salts (Mg or Ca) which contain a hydrophobic substituent. Examples of suitable acids are carboxylic acids, sulfonic acids, sulfinic acids, phosphonic acids, phosphonous acids, sulfuric acid monoesters, monoesters of sulfurous acid, phosphoric acid monoesters or diesters and monoesters or diesters of phosphorous acid, and also sulfated unsaturated carboxylic acid esters. Preferred acids are sulfated unsaturated carboxylic acid esters, sulfonic acids, phosphonic acids, sulfuric acid monoesters and phosphoric acid monoesters or diesters. Particular preference is given to sulfuric acid monoesters, dialkyl sulfosuccinates and phosphoric acid monoesters or diesters.

The acids preferably contain saturated or unsaturated hydrocarbon radicals having at least 6, preferably at least 8, C atoms and up to 30, preferably up to 20, C atoms. The hydrocarbon radicals can be interrupted by O, S, CO, -C(O)-O- and/or –C(O)-NH-, and/or be unsubstituted or substituted by -OH, -O-C_1-C_{20}-alkyl, -NH-C(O)-C_1-C_{20}-alkyl and/or -O-C(O)-C_1-C_{20}-alkyl. The hydrocarbon radicals can be selected from the group linear and branched alkyl, C_1-C_{20}-alkyl-substituted C_5-C_{12}-cycloalkyl and preferably C_5-C_8-cycloalkyl, C_1-C_{20}-alkyl-substituted C_6-C_{10}-aryl and C_5-C_{12}-cycloalkyl-substituted or C_6-C_{30}-polycycloalkyl-substituted C_1-C_{20}-alkyl. Polycycloalkyl preferably means condensed ring systems as can be found in the naturally occurring steroid and bile acids.

The anionic surfactant can correspond to the formulae II and IIa,

R-X (II),

R-C(O)-NH-R_6-SO_3H (IIa),

in which R is a saturated or unsaturated hydrocarbon radical having from 6 to 30 C atoms which is optionally interrupted by -O-, -S-, -CO-, -C(O)-O- and/or –C(O)-NH-, and/or is unsubstituted or substituted by -OH, -O-C_1-C_{20}-alkyl, -NH-C(O)-C_1-C_{20}-alkyl and/or -O-C(O)-C_1-C_{20}-alkyl, R_6 is C_2-C_4-alkylene and X is -SO_3H, -COOH or -OSO_3H, and also their sodium, potassium, magnesium and calcium salts. Examples of surfactants of the formula II are C_6-C_{20}-monoalkyl sulfates such as octyl sulfate, decyl sulfate, dodecyl sulfate, tetradecyl sulfate, hexadecyl sulfate and octadecyl sulfate, and also salts of fatty acids (Na oleate or Na caprate). Examples of surfactants of the formula IIa are 1-acylaminoethane-2-sulfonic acids, such as 1-octanoylaminoethane-2-sulfonic acid, 1-decanoylaminoethane-2-sulfonic acid, 1-dodecanoylaminoethane-2-sulfonic acid, 1-tetradecanoylaminoethane-2-sulfonic acid, 1-hexadecanoylaminoethane-2-sulfonic acid, and 1-octadecanoylaminoethane-2-sulfonic acid, and taurocholic acid and taurodeoxycholic acid. Bile acids and their salts, such as cholic acid, deoxycholic acid and sodium glycocholates, are also suitable.

Other suitable anionic surfactants are semiesters composed of polycarboxylic acids, such as malonic acid, succinic acid, glutaric acid, adipic acid, maleic acid and fumaric acid, and C_6-C_{20}-alkanols or C_6-C_{20}-alkenols, and their salts, for example sodium stearylsuccinate.

Particularly preferred anionic surfactants are alkali (alkaline earth) metal salts of saturated fatty acids such as sodium caprate or sodium laurate and unsaturated fatty acids, such as sodium oleate as well as alkyl sulfates, such as sodium lauryl sulfate and sodium cetyl sulfate. Other examples of particularly preferred compounds are sulfated castor oil and sodium dioctylsulfosuccinate.

Amphoteric surfactants are also suitable; among these, preference is given to natural or modified lecithins and phospholipids. The lecithins can be natural, partially hydrogenated or hydrogenated lecithins or sphingolipids. Natural lecithins are mixtures of different phospholipids. Examples of phospholipids are phosphatidylcholine, phosphatidyl ethanolamine, lysophosphatidyl choline, phosphatidyl glycerol, phosphatidic acid and phosphatidyl serine and their partially hydrogenated or completely hydrogenated derivatives. Examples of phospholipids containing defined fatty acids are 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dioleoyl-sn-glycero-3-phosphocholine, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, 1,2-dimyristoyl-sn-glycero-3-phospho-rac-glycerol, 1,2-dipalmitoyl-sn-

glycero-3-phospho-rac-glycerol and 1,2-distearoyl-sn-glycero-3-phospho-rac-glycerol. Preference is given to using lecithin and phosphatidyl choline

Examples of other known amphoteric surfactants are N-mono- or -dialkylated aminocarboxylic acids (betaines), with it being possible for the alkyl group to contain from 6 to 30, preferably from 8 to 20, C atoms. Examples are cocamidopropylbetaine and laurylbetaine (Amphoteen® 24). Other amphoteric surfactants are known from the class of the aminocarboxylic acids and their salts, and also as derivatives of imidazolines.

Natural lecithin is a preferred amphoteric surfactant.

Neutral surfactants are also known. These can, for example, be fatty alcohols and cholesterols, which are frequently used in combination with alkyl sulfates or polyethylene glycol monoalkyl esters.

Other known surfactants are monoesters or diesters composed of glycerol and C_8-C_{30}-carboxylic acids, in particular fatty acids, for example glycerol mono- or -distearate, glycerol mono- or -dioleate and glycerol mono- or -dipalmitate. Another group are ethoxylated partial fatty acid esters composed of polyols, such as ethylene glycol, propylene glycol, glycerol or pentaerythritol, and optionally hydrogenated polyoxy castor oils which can be obtained commercially as Chremophors®. Chremophor® EL and Chremophor® RH40 are preferred surfactant types.

Suitable neutral surfactants are also partial fatty acid esters of sorbitan which can be obtained commercially as SPAN® or ARLACEL®, and also partial fatty acid esters of sucrose.

Other suitable surfactants are fatty acid esters of polyols, such as ethylene glycol or pentaerythrol or polyethylene glycols, such as polyoxyethylene stearate, which esters can be obtained commercially in various types, for example as Myrj®.

Known neutral surfactants are also fatty alcohol ethers of polyoxyethylene, for example lauryl-, myristyl-, cetyl- and oleylpolyoxyethylene ethers. These can be obtained commercially in various types, for example as Brij®.

Sorbitan-based ethoxylated partial fatty acid esters are also known to be surfactants, with these surfactants being termed polysorbates and being offered for sale commercially in various types, for example as TWEEN®

Finally, polyethylene polypropylene glycols should also be mentioned. These surfactants are block copolymers containing blocks composed of polyoxyethylene and polyoxypropylene, with these block copolymers being termed poloxamers and being available commercially as Pluronics®. The blocks can be of varying chain length and the substances can be liquid to solid. Polyoxyethylene blocks can, for example, contain from 5 to 120, preferably from 10 to 100, oxyethylene units and polyoxypropylene blocks can contain from 10 to 80, and preferably from 10 to 50, oxypropylene units. The chain lengths of the blocks and the molecular weight of the substance can be used to achieve desired properties in a selective manner. Poloxamers 124, 188 and 407 are preferred examples.

Preferred neutral surfactants are block copolymers composed of polyoxyethylene and polyoxypropylene, partial fatty acid esters of sorbitan, ethoxylated partial fatty acid esters of sorbitan, fatty alcohol ethers and fatty acid esters of polyoxyethylenes and hydrogenated, polyethoxylated castor oils.

Suitable surfactants are described, for example, in pharmacopoeias such as USP25/NF20 or can be identified from the literature, in this present case for example, from Martindale, thirty-second editlon 1999, pages 1324-1329 and 1468-1469.

The composition according to the invention can be produced in a simple manner by mixing the components. The composition can be liquid to oily, semisolid or solid. The consistency of the composition depends essentially on the choice of surfactant or combination of surfactants and the quantitative composition. Known methods for mixing the components are dry mixing of pulverulent components, melting methods, and solution methods, involving dissolving the components and subsequently removing the solvents.

Solvents are expediently selected such that they can be removed virtually completely. Suitable solvents are water and organic solvents, particularly polar organic solvents, which can also be used as mixtures of at least two solvents. Examples of pharmaceutically customary solvents are halohydrocarbon (methylene chloride); ketones (acetone); alcohols

(methanol, ethanol, n- or i-propanol, or n- or i-propanediol); nitriles (acetonitrile); and tertiary amines (N-methylpyrrolidine).

Because of its increased bioavailability, the composition according to the invention is outstandingly suitable for producing forms for oral administration. Because of the increased bioavailability, it is possible to provide doses which are physiologically harmless as far as the active compound and surfactant are concerned.

The invention also relates to an oral dosage form which comprises a composition according to the invention.

Examples of oral dosage forms are tablets or sugar-coated tablets, capsules composed of hard or soft gelatin or starch, and potable preparations.

Depending on the intended therapy, i.e. single or repeated consecutive and chronologically delayed administration, the oral administration form can comprise a renin inhibitor in quantities of from 10 to 600 mg, preferably of from 30 to 300 mg, and in particular of from 50 to 200 mg.

The skilled person is familiar with the production of tablets, sugar-coated tablets, capsules and potable preparations and the auxiliary substances which are required for this purpose.

Potable preparations principally comprise water. In addition, they can comprise physiologically tolerated solvents, for example alkanols such as ethanol. Customary thickeners can be used in order to stabilize suspensions.

Capsules can be filled directly with the composition according to the invention. However, the composition of the material which is used to fill the capsules can also comprise customary pharmaceutical auxiliary substances such as fillers, binders, disintegrants, lubricants and flavourings.

It is possible to use customary auxiliary substances, such as binders, fillers, lubricants and flavourings, for formulating tablets and sugar-coated tablets. These auxiliary substances are known and are therefore not described in detail.

All the solid administration forms can be provided with a coating of any given functionality. Pharmaceutically customary auxiliary substances, such as semisynthetic or fully synthetic film-forming agents, and suitable additives, such as plasticizers and dye pigments, have also to be provided for this purpose.

The invention also relates to a method for increasing the bioavailability of non-peptide renin inhibitors which is characterized in that the said renin inhibitor is mixed with at least one physiologically tolerated anionic surfactant or at least one physiologically tolerated neutral or amphoteric surfactant or with a mixture consisting of at least two of these surfactants.

The composition according to the invention makes it possible to produce oral forms for administering renin inhibitors which, because of an increased bioavailability, can be used for higher dosages and are practical for a patient.

The following examples explain the invention in more detail.

A) Producing compositions

Example A1: Producing a powder mixture
75 g of SPP100B and 75 g of sodium lauryl sulfate are weighed into a mixing box and mixed for 10 minutes in a Turbula mixer. The resulting mixture is brushed through a sieve having a mesh aperture of 0.5 mm. The sieve mixture is then once again agitated for 10 minutes in the Turbula mixer.
The desired quantities of these powders are apportioned and aliquoted, for example, into bottles. Prior to administration, the preparation is dissolved in water or another suitable physiologically well-tolerated liquid.

Example A2: Producing a powder mixture
75 g of SPP500A and 75 g of sodium laurate are weighed into a mixing box and mixed for 10 minutes in a Turbula mixer. The resulting mixture is brushed through a sieve having a mesh aperture of 0.5 mm. The sieved mixture is finally agitated once again in the Turbula mixer for 10 minutes.

The desired quantities of these powders are apportioned and aliquoted, for example, into bottles. Prior to administration, the preparation is suspended or dissolved in water or another suitable physiologically well-tolerated liquird.

Example A3: Melting method

100 g of Poloxamer 188 are weighed into a glass flask and melted at 70°C in a waterbath. 25 g of SPP500A are added to the melt. This mixture is cooled while being stirred continuously and then suitably comminuted. Portions depending on the dose are packaged into suitable receptacles or processed into oral administration forms.

Example A4: Solution method

75 g of SPP100B are kneaded with 7.5 g of sorbitan monooleate and 15 g of Polysorbat 80, dissolved in 15 ml of 99% ethanol. The resulting mass is dried at 50°C in vacuo until a constant weight Is reached. Portions depending on the dose are packaged into suitable receptacles or processed to produce oral administration forms.

B) Producing oral administration forms

Example B1: Producing hard gelatin capsules

One capsule contains:

SPP100B	83 mg
Microcrystalline cellulose	95 mg
Crospovidone (a polyvinylpyrrolidone)	26 mg
Colloidal silicon dioxide	2 mg
Sodium lauryl sulfate	30 mg
Magnesium stearate	4 mg

The active compound, the filler, the disintegrant, the flow regulating agent and the surfactant are mixed in one operational step. The mixture is sieved and mixed once again in the dry. Finally, magnesium stearate is added as lubricant and admixed for 3 minutes. In conclusion, the mass, corresponding to 240 mg, is aliquoted into size 0 capsules.

Example B2: Producing soft gelatin capsules

One capsule contains:

SPP100B	75 mg
Hydrogenated vegetable oil	50 mg
Medium-chain triglycerides (MCT)	250 mg

Lecithin	150 mg
Glycerol stearate	50 mg
Yellow wax	30 mg
Oleic acid	10 mg
Ascorbyl palmitate	5 mg

All the auxiliary substances are weighed into a glass vessel. The mass is heated and stirred until a clear solution is obtained. The melt is then homogenized for 10 minutes. SPP100B is added and the mass is brought to a suitable temperature for aliquoting, while being subjected to further stirring and homogenization, and encapsulated in soft gelatin.

C) Application examples:

Example C1: Determining the bioavailability

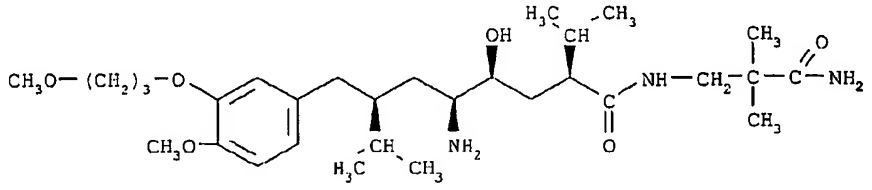
The bioavailability of a powder mixture composed of surfactant and active compound is compared with that of SPP100B on its own in an absorption study carried out in rats. The rat model is chosen since, in this model, the absorption of the active compound is low and small quantities of active compound can be investigated.

The active compound, or a mixture of 2 parts of SPP100B and 1 part of sodium lauryl sulfate, is in each case administered to 10 rats. The plasma levels are measured over a period of 24 hours after administering the dose. In this model, it is found that adding this surfactant to the renin inhibitor significantly increases oral bioavailability.

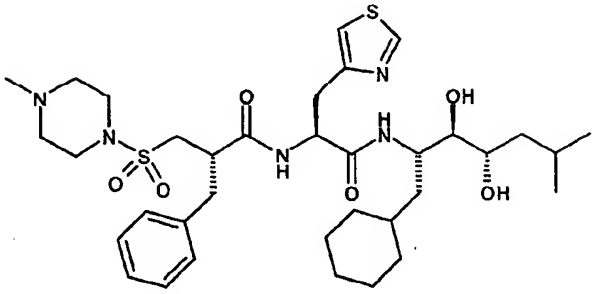
Patent claims:

1. Composition comprising (1) a non-peptide renin inhibitor which is poorly soluble to readily soluble in water and (2) at least one physiologically tolerated anionic surfactant, at least one physiologically tolerated amphoteric surfactant, at least one physiologically tolerated neutral surfactant, or a mixture of at least two of these surfactants, with the quantity of a readily soluble renin inhibitor being at least 10% by weight, and the quantity of a poorly soluble renin inhibitor being at least 35% by weight, based on the composition.

2. Composition according to claim 1, characterized in that the renin inhibitor comprises compounds of the formula Ia or its physiologically tolerated salts or of the formulae A, B, C, F, G or H:



(Ia),



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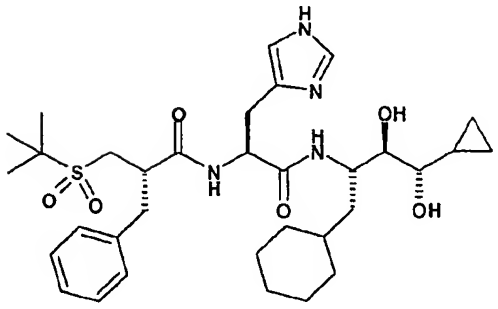
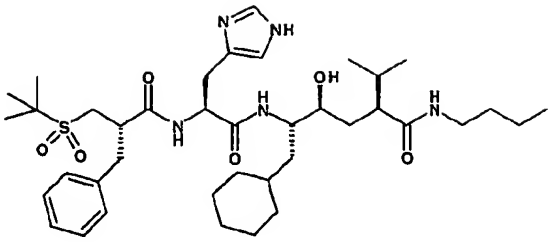
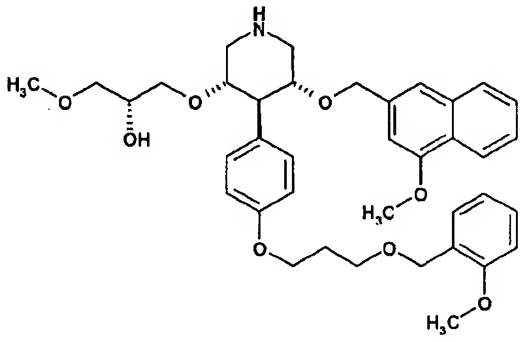


(B).



(C).



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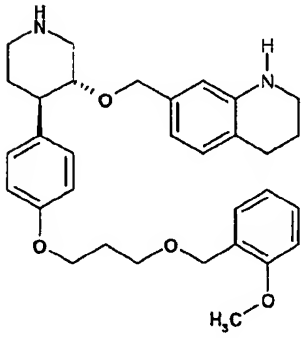
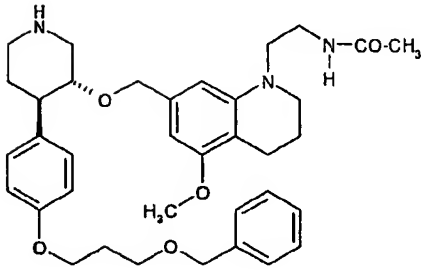


(G),



(H).

3. Composition according to claim 1 characterized in that the quantity of water-soluble renin inhibitors is from 10 to 90% by weight, based on the composition.

4. Composition according to claim 3, characterized in that the quantity of water-soluble renin inhibitors is from 50 to 90% by weight, based on the composition.

5. Composition according to claim 1, characterized in that the quantity of poorly soluble renin inhibitors is from 40 to 90% by weight, based on the composition.

6. Composition according to claim 5, characterized in that the quantity of poorly soluble renin inhibitors is from 60 to 90% by weight, based on the composition.

7. Composition according to claim 1, characterized in that the anionic surfactants are organic acids, and their physiologically tolerated salts of alkali metals or alkaline earth metals, which contain a hydrophobic substituent.

8. Composition according to claim 7, characterized in that it is sodium lauryl sulfate, sodium cetyl sulfate, sulfated castor oil or sodium dioctyl sulfosuccinate.

9. Composition according to claim 1, characterized in that the amphoteric surfactants are natural or modified lecithins, phospholipids and betains.

10. Composition according to claim 9, characterized in that the amphoteric surfactants are natural lecithins.

11. Composition according to claim 1, characterized in that the neutral surfactants are selected from the group monoesters or diesters composed of glycerol and C_8-C_{30}-carboxylic acids, ethoxylated partial C_8-C_{30}-carboxylic acid esters of polyols, optionally hydrogenated polyoxyl castor oils, partial C_8-C_{30}-carboxylic acid esters of sorbitan, C_8-C_{30}-carboxylic acid esters of polyols, C_8-C_{30}-alkyl ethers of polyoxyethylene, ethoxylated C_8-C_{30}-carboxylic acid esters of sorbitan and polyethyleneoxy/polypropyleneoxy block copolymers.

12. Oral administration form comprising a composition according to claim 1.

13. Oral administration form according to claim 12, characterized in that it comprises tablets, sugar-coated tablets, capsules or a potable preparation.

14. Oral administration form according to claim 12, characterized in that the renin inhibitor is present in a quantity of from 10 to 600 mg, based on the administration form.

15. Method for increasing the bioavailability of non-peptide renin inhibitors, characterized in that the said renin inhibitor is mixed with at least one physiologically tolerated anionic surfactant, with at least one physiologically tolerated amphoteric surfactant or at least one physiologically tolerated neutral surfactant, or with a mixture of at least two of these surfactants.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/50266

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K31/425 A61K31/415 A61K38/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 523 289 A (ALVAREZ FRANCISCO J ET AL) 4 June 1996 (1996-06-04) claims 1,3 examples 1A,-1D column 24; table 1 ---	1-15
Y	EP 0 031 603 A (AMERICAN CYANAMID CO) 8 July 1981 (1981-07-08) page 3, line 9 -page 5, line 2 ---	1-15
Y	US 6 346 537 B1 (HATA TAKEHISA ET AL) 12 February 2002 (2002-02-12) column 1, line 4-8 column 2, line 4-7 column 8, line 52 -column 10, line 16 --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2003	28/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Peris Antoli, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/50266

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y A	US 2001/007663 A1 (VON CORSWANT CHRISTIAN) 12 July 2001 (2001-07-12) column 1, paragraphs 5,9	1-15
Y	LECLUYSE EDWARD L ET AL: "In vitro models for selection of development candidates. Permeability studies to define mechanisms of absorption enhancement" ADV DRUG DELIVERY REV;ADVANCED DRUG DELIVERY REVIEWS JAN 15 1997 ELSEVIER SCIENCE B.V., AMSTERDAM, NETHERLANDS, vol. 23, no. 1-3, 15 January 1997 (1997-01-15), pages 163-183, XP001155996 cited in the application page 166, column 2, paragraph 1 -page 167, column 1, paragraph 3 page 176, column 1	1-15
A	KIM D-C ET AL: "EVALUATION OF THE BILE ACID TRANSPORTER IN ENHANCING INTESTINAL PERMEABILITY TO RENIN-INHIBITORY PEPTIDES" JOURNAL OF DRUG TARGETING, HARWOOD ACADEMIC PUBLISHERS GMBH, DE, vol. 1, no. 4, 1993, pages 347-359, XP000564343 ISSN: 1061-186X abstract	1-15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-15

Present claims 1-15 relate to compositions comprising (1) compounds defined by reference to a desirable characteristic or property, namely renin-inhibitors which are further defined as being non-peptide and being poorly to readily soluble in water; and (2) surfactants, which as such relate to an extremely large number of possible compounds.

Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of renin-inhibitors and surfactants. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, with due regard to the idea underlying the subject matter of the claims, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to renin-inhibitors as specified in claim 2, to surfactants in general and to those specific surfactants used in the examples of the aplication.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/50266

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-15
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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